REMARKS

Claims 4-10, 12-17, 19-22, 25, 26, and 28 are pending in this application. Claims 12-15 and 17 have been withdrawn from consideration, as drawn to non-elected matter. Claims 1-3, 11, 18, 23, 24, and 27 are canceled without prejudice or disclaimer. Claims 9, 16, 19, 20-22, 26, and 28 are amended herein.

Claims 9, 16, and 26 have been amended to recite "anti-parathyroid hormone related protein 1-34 (anti-PTHrP (1-34)) antibody." Support for that amendment can be found throughout the specification, *e.g.*, in Reference Example 1 on pages 23-24 and Reference Example 2 on pages 24-30. Claims 9, 16, and 26 have been further amended to recite, "wherein the antibody neutralizes parathyroid hormone related protein 1-34." Support for that amendment can be found in the specification, *e.g.*, on page 16, lines 24-25 and in Reference Example 5 on pages 67-68.

Claim 16 has also been amended to recite, "wherein the antibody, or binding fragment thereof, binds specifically to SEQ ID NO: 75" and "thereby maintaining or increasing low vasopressin levels." Support for those amendments can be found throughout the specification, *e.g.*, on page 2, lines 13-15 and Example 1 on pages 23-24.

Claim 19 has been amended to recite, "wherein said modification is selected from amino acid substitution and chemical modification." Support for that amendment can be found, *e.g.* on pages 14, 57-62, 64-66, and 67-69 of the specification.

Claim 20 has been amended to correct claim dependency and to recite, "wherein the antibody is a humanized, human, or chimeric antibody." Support for that

amendment can be found in the specification, *e.g.*, at the paragraph bridging pages 3 and 4.

Claim 21 has been amended to recite, "wherein the antibody is produced by the hybridoma deposited as FERM BP-5631." Support for that amendment can be found, *e.g.*, on page 5, lines 7-11 of the specification.

Finally, claims 22 and 28 have been amended to correct claim dependency. Thus, no new matter has been added by these amendments.

I. Formal Matters

Applicants acknowledge with appreciation that claims 16 and 18-22 have been rejoined with the elected group of claims. Applicants also note that the following rejections were not maintained in the present Office Action and are, therefore, deemed withdrawn:

1. Rejection of claims 1, 5, 7-11, and 23-25, and 27 under 35 U.S.C. § 112 ¶ 1 for enablement; and
2. Rejection of claims 1, 5, 7-11, and 23-25 under 35 U.S.C. § 112 ¶ 1 for written description.

II. Rejections Under 35 U.S.C. § 112 ¶ 1

A. Enablement

Claims 4, 16, 18-20, and 22 are rejected under 35 U.S.C. § 112 ¶ 1 as allegedly lacking enablement. Applicants respectfully traverse.

Claim 18 has been canceled, without prejudice or disclaimer, rendering the rejection of that claim moot. With regard to claim 16, the Office argues that the specification fails to provide support for "a method of inhibiting the binding between PTHrP and a receptor thereof comprising providing any 'substance.'" Office Action at p. 3. Without acquiescing to the rejection, Applicants have amended claim 16 to remove the term "substance." As currently amended, claim 16 recites, "[a] method of inhibiting the binding between PTHrP and a receptor thereof comprising providing an anti-parathyroid hormone related protein 1-34 (anti-PTHrP (1-34)) antibody." As the Office admits, the specification is enabling for an "antibody or antigen binding fragment thereof that binds specifically to the N-terminal 1-34 of human PTHrP consisting of SEQ ID NO:75." Office Action at p. 2. Accordingly, currently amended claim 16 recites embodiments which the Office acknowledges are enabled. Thus, Applicants respectfully request that the rejection of claim 16 and its dependent claims 20 and 22 be withdrawn.

Since currently amended claim 19 is similar to claim 4, Applicants will address these claims together. In rejecting claim 4, the Office argues that the specification fails to provide enablement for "any amino acid substitution" or "any modification." Office Action at p. 4. Specifically, the Office argues that undue experimentation is required because, "[g]iven the unlimited number of amino acid substitution, it is unpredictable which antibody modification is associated with maintaining low vasopressin and which modification is associated with increasing low vasopressin level." Office Action at p. 4. The Office also argues that "[t]he state of the prior art . . . is such that chemical

modification such as reduction and alkylation affect the confirmation of the protein-antibody interaction." *Id.* Applicants respectfully traverse.

In view of the guidance provided in the specification, one of skill in the art could determine which amino acid substitutions or chemical modifications maintain low vasopressin levels and/or increase low vasopressin levels without undue experimentation. In *Atlas Powder*, the court held that the specification must enable a person of ordinary skill in the art to practice only a single use of the claimed invention without undue experimentation. *Atlas Powder v. E.I. Du Pont de Nemours & Co.*, 750 F.2d 1569 (Fed. Cir. 1984). Making the claimed embodiments and screening them for function is acceptable, as long as the experimentation is not undue. *Id* at 1576. Furthermore, "[t]he test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." M.P.E.P. § 2164.06 (8th Ed., Rev. 5, Aug. 2006) (emphasis added) (citing *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1998)).

The seminal case of *In re Wands* provides a classic example of an enabled invention in a biotechnology field the court considered potentially unpredictable, that of a monoclonal antibody for a particular antigen. In *Wands*, the specification exemplified four successful hybridoma lines out of the 143 lines synthesized. The court acknowledged that the methods required to make hybridoma cells at the time of the invention were complicated and time-consuming and that the outcome of screens to find the claimed monoclonal antibodies would not be predictable. However, the court held

that despite the unpredictability, the specification provided sufficient directions for one to proceed.

As in *Wands*, the instant application provides ample guidance for synthesizing modified antibodies comprising amino acid substitutions or chemical modifications. *See*, *e.g.*, Reference Example 4, pp. 47-67; and p. 13, ln. 28-p. 14, ln. 4. Moreover, the specification teaches assays for determining whether the modified antibodies retain antigen-binding function and neutralizing activity. *See*, *e.g.*, Reference Example 4, pp. 47-67 and Reference Example 5, pp. 67-69. Finally, Applicants have provided examples of nineteen modified antibodies and have disclosed the regions of these antibodies which tolerate modification. *Id.* Thus, in view of the guidance provided in the specification, the experimentation required to make and screen the modified antibodies for the ability to neutralize PTHrP are within the skill of the ordinary artisan. Accordingly, claims 4 and 19 meet the enablement requirement.

The Office also appears specifically concerned that "the unlimited number of amino acid substitution[s]" makes the inventions of claim 4 and currently amended claim 19 unpredictable. However, *In re Angstadt* held that generic claims in an unpredictable art are acceptable. *In re Angstadt*, 537 F.2d 498, 190 U.S.P.Q. 214 (C.C.P.A. 1976). The question in *Angstadt* was whether a claim generically reciting a "catalyst" was enabled, or whether only the specific catalysts used in the patent's text were enabled. The court explained, "[t]he question, then, is whether in an unpredictable art, section 112 requires disclosure of a test with every species covered by the claim. To require such a complete disclosure would apparently necessitate a patent application or

applications with 'thousands' of examples or the disclosure of 'thousands' of catalysts . . . such a requirement would force an inventor seeking adequate patent protection to carry out a prohibitive number of actual experiments. This would tend to discourage inventors from filing patent applications in an unpredictable area since the patent claims would have to be limited to those embodiments which are expressly disclosed." *Id.* at 218 (footnote omitted). Thus, the court held that the patent's disclosure was sufficient to point an experimenter toward appropriate examples falling within the generically claimed class.

As in *Angstadt*, the instant specification provides sufficient examples of the species covered by the claim. Specifically, nineteen modified antibodies, comprising 50 amino acid substitutions are exemplified. *See, e.g.*, Reference Example 4, pp. 47-67. In addition, the specification teaches regions of the antibodies which tolerate modification and exemplary modifications that result in wild-type neutralizing activity. *Id.* and Reference Example 5, pp. 67-69. Under the standard established in *Angstadt*, Applicants need not demonstrate each and every operable embodiment of claims 4 and 19. Rather, the test is whether undue experimentation is required to make and screen the embodiments. In view of the ample guidance provided by the specification, Applicants submit that the ordinary artisan could practice the inventions of claim 4 and currently amended claim 19 without undue experimentation.

Accordingly, Applicants respectfully request that the enablement rejection of claims 4 and 19 be withdrawn.

B. Written Description

Claims 4, 16, 18-20, 22, and 28 are rejected under 35 U.S.C. § 112 ¶ 1 as allegedly failing to comply with the written description requirement. Applicants respectfully traverse.

Claim 18 has been canceled, without prejudice or disclaimer, rendering the rejection of that claim moot. Regarding claim 28, the Office argues, "[t]he specification at page 23 lines 14-15 discloses the *immunogen* (PTHrP1-34) was conjugated to a carrier protein thyroglobulin, NOT the anti-PTHrP antibody that binds specifically to SEQ ID NO: 75." Office Action at p. 10 (emphasis in original). Without acquiescing to the rejection, and solely to facilitate prosecution, claim 28 has been amended to remove the phrase "thyroglobulin conjugation." Accordingly, Applicants respectfully request that the written description rejection of claim 28 be withdrawn.

In rejecting claim 16, the Office argues, "there is inadequate written description about the structure associated with function of any 'substance.'" Office Action at p. 10. Without acquiescing to the rejection, Applicants have amended claim 16 to remove the term "substance." As currently amended, claim 16 recites, "[a] method of inhibiting the binding between PTHrP and a receptor thereof comprising providing an anti-parathyroid hormone related protein 1-34 (anti-PTHrP (1-34)) antibody." As the Office admits, the specification discloses an "antibody that binds specifically to the N-terminus 1-34 of human PTHrP consisting of the amino acid sequence of SEQ ID NO:75 . . . [and] inhibits the binding between human PTHrP and its receptor." Office Action at p. 11. Accordingly, currently amended claim 16 recites limitations which the Office

acknowledges are supported by the specification. Thus, Applicants respectfully request that the rejection of claim 16 and its dependent claims 20 and 22 be withdrawn.

Since currently amended claim 19 is similar to claim 4, Applicants will address these claims together. In rejecting claim 4, the Office argues that the specification does not reasonably provide written description for any modified antibody, any amino acid substitution, or any chemical modification. Specifically, the Office argues, "the disclosure fails to provide a representative number of . . . modified form of the fragment, anti-PTHrP antibody, and modified fragment thereof to describe the genus for the claimed method." Office Action at p. 11. Applicants respectfully traverse.

"The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus." M.P.E.P. § 2163, citing *University of California v. Eli Lilly*, 119 F.3d 1559, 1568 (Fed. Cir. 1997). Moreover, "[d]escription of a representative number of species does not require the description to be of such specificity that it would provide individual support for each species that the genus embraces." *Id.*

Applicants submit that the specification provides sufficient disclosure of a representative number of species encompassed by claim 4 and currently amended

claim 19 to satisfy the written description requirement. As discussed above, Reference Example 4 on pages 47-67 of the specification discloses nineteen modified antibodies comprising 50 amino acid substitutions. The sequences of these antibodies are also disclosed in the Sequence Listing. In addition, the specification identifies several structural regions of the antibodies which tolerate modification. For example, "when the L-chain was either m/hMBC1Iaλ or m/hMBC1Ldλ, . . . FR3 and FR4 have no problem as humanized antibodies but FR1 and FR2 contain amino acid residue(s) that need to be replaced." Specification, p. 65, ll. 15-20. Likewise, "when the L-chain was hmmMBC1L9λ, . . . FR1 has no problem as a humanized antibody but FR2 contains amino acid residue(s) that need to be replaced." *Id.* at ll. 22-26. Furthermore, the specification identifies exemplary modifications that result in wild-type neutralizing activity. For example, "those antibodies having L-chain versions . . . (in which the 91-position tyrosine was replaced by isoleucine) exhibited the similar neutralizing activity to that of the chimeric antibody." Specification, p. 68, ll. 24-28.

As discussed above, to satisfy the written description requirement, Applicants need not demonstrate each and every species of claims 4 and 19. Rather, Applicants need only provide adequate description of the structural or functional characteristics of a representative number of species. In view of the nineteen exemplary modified antibodies disclosed in the specification and the guidance provided therein regarding regions of the antibodies which tolerate modification, Applicants submit that the specification provides adequate support for the inventions of claim 4 and currently amended claim 19.

Accordingly, Applicants respectfully request that the written description rejection of claims 4 and 19 be withdrawn.

III. Rejections Under 35 U.S.C. § 102

A. *Yamamoto*

Claims 16 and 19 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Yamamoto, S., et al., "Parathyroid Hormone-Related Peptide-(1-34) [PTHrP=(1-34)] Induces Vasopressin Release from the Rat Supraoptic Nucleus *in Vitro* through a Novel Receptor Distinct from a Type I or Type II PTH/PTHrP Receptor," Endocrinology, 138(5):2066-72 (1997) ("*Yamamoto*"). Applicants respectfully traverse.

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." M.P.E.P. § 2131. As currently amended, claims 16 and 19 recite that the substance capable of inhibiting binding is an anti-PTHrP antibody. In contrast, *Yamomoto* does not disclose the administration of a PTHrP antibody to maintain or increase vasopressin level, but only teaches the use of a PTHrP(1-34) fragment. Thus, *Yamomoto* cannot anticipate currently amended claims 16 and 19 because it fails to teach all of the limitations of those claims.

Accordingly, Applicants respectfully request that the rejection of claims 16 and 19 over *Yamomoto* be withdrawn.

B. U.S. Patent No. 6,903,194

Claims 4-10, 16, 18, 20-22, and 26 are rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by U.S. Patent No. 6,903,194 to Sato et al. ("the '194 patent"). Specifically, the Office argues, "Given the reference method uses the same antibody to treat the same patient population via the same mechanism . . . the reference method inherently has the same effect such as maintaining low vasopressin level." Office Action, p. 15. Applicants respectfully traverse.

Applicants respectfully submit that the '194 patent does not inherently teach methods of maintaining or increasing vasopressin levels, as required by claims 4-10, 16, 18, 20-22, and 26. "In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." M.E.P.P. § 2112, citing *Ex parte Levy*, 17 U.S.P.Q.2d 1461, 1464 (Bd. Pat. App. & Inter. 1990) (emphasis in original). Furthermore, inherency "may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." *In re Robertson*, 169 F.3d 743, 745 (Fed Cir. 1999) (emphasis added).

There is nothing in the record to demonstrate that any of the hypercalcemia patients discussed in the '194 patent were suffering from low vasopressin levels. The '194 patent does not mention vasopressin levels or the effect of an anti-PTHrP antibody on vasopressin level. Thus, the Office has not provided a basis in fact and/or technical reasoning to support its position that "the reference method inherently has the same

effect as maintaining low vasopressin level as claimed." Office Action at p. 15. Without such support, it is impossible to state that administration of a PTHrP antibody necessarily maintained or increased the low vasopressin levels. The unlikely and purely coincidental possibility that some patients may be suffering from both hypercalcemia and low vasopressin level and that both conditions may be treated by administration of a PTHrP antibody does not legally suffice to show anticipation.

Accordingly, Applicants respectfully request that the rejection of claims 4-10, 16, 18, 20-22, and 26 over the '194 patent be withdrawn.

C. CA 2,266,332

Claims 4-10, 16, 18, 20-22, and 26 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Canadian Patent No. 2,266,332 to Sato et al. ("the '332 patent"). Specifically, the Office argues, "Given the reference method uses the same antibody to treat the same patient population via the same mechanism . . . the reference method inherently has the same effect such as maintaining low vasopressin level." Office Action, p. 16. Applicants respectfully traverse.

First, Applicants would like to point out that the '332 patent was also published as U.S. Patent No. 6,903,194, discussed above. Accordingly, all of the arguments discussed above for the novelty of claims 4-10, 16, 18, 20-22, and 26 in view of the '194 patent also apply to the '332 patent. In addition, the Office states that the '332 patent "teaches a method of treating at least one symptom caused by a decrease in vasopressin levels." Office Action, p. 16. However, as discussed above for the '194 patent, the '332 patent also does not mention vasopressin levels or the effect of an anti-

PTHrP antibody on vasopressin level. The Office's particular citation to page 2, lines 7-24 and page 135 of the '332 patent does not even mention vasopressin.

Accordingly, for these reasons and those discussed above under "Section B," Applicants respectfully request that this rejection of claims 4-10, 16, 18, 20-22, and 26 over the '332 patent be withdrawn.

IV. Rejections Under 35 U.S.C. § 103(a)

A. The '194 Patent or The '332 Patent in view of *Kitamura*

In items 16 and 18 of the Office Action, claims 4, 9, 10, 16, 19, 25, 26, and 28 are rejected as allegedly being obvious over the '194 patent or the '332 patent in view of Kitamura, K., et al., "Polyethylene Glycol Modification of the Monoclonal Antibody A7 Enhances its Tumor Localization," Biochem. Biophys. Res. Commun., 171(3):1387-94 (1990) ("*Kitamura*"). Since the '194 patent and the '332 patent have identical disclosures, Applicants will traverse these rejections together.

As discussed above, the '194 and '332 patents fail to teach methods of maintaining or increasing vasopressin levels, as required by claims 4, 9, 10, 16, 19, 25, 26, and 28. *Kitamura*, which teaches a PEG-conjugated antibody fragment, does not discuss modulating vasopressin levels and thus, fails to cure the defects in the '194 and '332 patents. As such, the Office has failed to establish a *prima facie* case of obviousness because all of the claim limitations are not taught or suggested by the cited combinations of references.

In addition, Applicants would like to correct the Office's apparent misinterpretation of the '194 patent. On page 19 of the Office Action, the Office argues:

> The '194 patent teaches antibody such as monoclonal, humanized, chimeric or human antibody that binds to PTHrP of SEQ ID NO: 75 is useful for treating the symptoms associated with malignancy such as hypercalcemia, reduction of water concentrating ability due to lesion of the renal distal tubules lea[d]s to hyperuresis (poluria), and anorexia and nausea accompanied with dehydration which all resulted from low levels of vasopressin levels (see col. 2, lines 42-57, in particular).

However, as discussed above, the '194 patent does not discuss vasopressin levels or the effect of an anti-PTHrP antibody on vasopressin level. The Office's particular citation to column 2, lines 42-57 of the '194 patent does not even mention vasopressin.

Accordingly, for the reasons discussed above, Applicants respectfully request that the rejection of claims 4, 9, 10, 16, 19, 25, 26, and 28 over the '194 or '332 patents in view of *Kitamura* be withdrawn.

B. The '194 Patent or The '332 Patent in view of *Harlow* or U.S. Patent No. 4,946,778

In items 17 and 19 of the Office Action, claims 25 and 26 are rejected as allegedly being obvious over the '194 patent or the '332 patent in view of Harlow, I., et al., "Antibodies: A Laboratory Manual," Cold Spring Harbor Laboratory Press, pp. 626-29 (1990) ("*Harlow*") or U.S. Patent No. 4,946,778 to Ladner et al. ("the '778 patent"). Since the '194 patent and the '332 patent have identical disclosures, Applicants will traverse these rejections together.

As discussed above, the '194 and '332 patents fail to teach methods of maintaining or increasing vasopressin levels, as required by claims 25 and 26. Neither *Harlow*, which teaches a method of producing an antibody fragment, nor the '778 patent, which teaches a method of producing single chain antibodies, discusses modulating vasopressin levels and thus, both references fail to cure the defects in the '194 and '332 patents. As such, the Office has failed to establish a *prima facie* case of obviousness because all of the claim limitations are not taught or suggested by the cited combinations of references.

In addition, Applicants would like to correct the Office's apparent misinterpretation of the '194 patent. On page 20 of the Office Action, the Office argues, "The '194 patent teaches the PTHrP antibody is useful for treating at least one symptom such as hypercalcemia, polyuria, or dehydration, that [is] caused by cancer (see col. 1, lines 42-61, in particular) which resulted in inherent low vasopressin levels (see col. 60, line 6-18, in particular)." However, as discussed above, the '194 patent does not discuss vasopressin levels or the effect of an anti-PTHrP antibody on vasopressin level. Nor does the Office provide a basis in fact and/or technical reasoning to support its position that the '194 patent inherently teaches methods of maintaining or increasing vasopressin levels. The Office's particular citation to column 60, lines 6-18 of the '194 patent does not even mention vasopressin.

Accordingly, for the reasons discussed above, Applicants respectfully request that this rejection of claims 25 and 26 be withdrawn.

V. Nonstatutory Obviousness-Type Double Patenting Rejections

On pages 24-28 of the Office Action, the Office issues the following nonstatutory obviousness-type double patenting rejections:

- Claims 4-10, 16, 18, 20-22, and 26 are rejected as allegedly not being patentably distinct over claim 11 of the '194 patent;
- Claims 4, 9, 10, 16, 19, 25, 26, and 28 are rejected as allegedly not being patentably distinct over claim 11 of the '194 patent in view of *Kitamura*; and
- Claims 25 and 26 are rejected as allegedly not being patentably distinct over claim 11 of the '194 patent in view of *Harlow* or the '778 patent.

Applicants will consider filing a terminal disclaimer to overcome these rejections once patentable subject matter has been indicated in this case. Until then, Applicants request that the Office hold the rejection in abeyance.

Conclusion

In view of the foregoing amendments and remarks, Applicants respectfully request reconsideration and reexamination of this application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to Deposit Account No. 06-0916.

Respectfully submitted,

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